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EXAMINER
PORTNER, VIRGINIA ALLEN

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1645	31

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/259,658	Applicant(s) Colyer
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 17, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-12, 14, 15, 17, 18, 20, and 21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12, 14, 15, 17, 18, 20, and 21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 28
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1, 17 and 21 have been amended.

Claims 13, 16 and 19 have been canceled.

Claims 1-12, 14-15, 17-18 and 20-21 are pending and under consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections Withdrawn

2. Claim 1 rejected under 35 U.S.C. 112, second paragraph for reciting the word "enzyme", when none of the methods steps detect the presence of the enzyme in the sample defined in the preamble of the claim, in light of the amendment of claim 1 to define an indirect presence of a modifying enzyme.
3. Claim 1 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase in subsection c) "the immobilized polypeptide with the second polypeptide", in light of the amendment of claim 1 to recite "a second, binding partner polypeptide'>
4. Claim 1, subsection d) rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "contacting said immobilized polypeptide and said binding partner polypeptide with said sample", in light of the amendment of claim to recite specific types of covalent modification.
5. Claim 1 in subsection e) rejected under 35 U.S.C. 112, second paragraph for reciting phrase "assaying the modification of at least one of the polypeptides", in light of the amendment of claim 1 to define that covalent modification of either polypeptide can be measured, and the type of modification has been defined.
6. Claim 13 rejected under 35 U.S.C. 112, second paragraph for reciting the term "agent" , has been obviated through cancellation of the claim.
7. Claim 15 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "measured in real time", in light of Applicant pointing out the definition of this phrase provided by the instant specification.
8. Claim 17 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "said binding partner polypeptide", in light of the amendment of claim 17 to recite "second binding partner polypeptide."
9. Claim 17 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "is required for said association", in light of the amendment of claim 17 to define the specific covalent modification for association between the polypeptides.

10. Claim 17 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "the binding of the polypeptides is detectable" in light of the amendment of the claim to define the binding of the two polypeptides "to each other" is detectable.

11. Claim 21 rejected under 35 U.S.C. 112, second paragraph for reciting the step of providing first and second polypeptides and a test sample, but they are not combined, in light of the amendment of claim 21 to recite the additional step of "contacting".

12. Claim 17 rejected under 35 U.S.C. 102(e) as being anticipated by Mills (US Pat. 5,773,592) for reasons of record in papers number 10, 12 and response to arguments below, in light of the amendment of claim 17 to be a specific type of covalent modification.

13. Claims 1-3, 8, 10, 12, 14-21, as previously applied to claims 1-2, 14, 16, 18 and 20, are rejected under 35 U.S.C. 102(b) as being anticipated by Avruch et al (US Pat. 5,582,995), in light of Applicant's arguments and the amendment of claims to recite a new combination of limitations that determine the covalent modification of one of the polypeptides to detect the modifying enzyme.

14. claims 1-2, 5, 10-11, 14-15, 18, 20 and 21, as previously applied to claims 1-2, 10-11 and 20, are rejected under 35 U.S.C. 102(e) as being anticipated by Josiah et al (6,146,842), in light of Applicant's arguments and the amendment of claims to recite a new combination of limitations that determine the covalent modification of one of the polypeptides to detect the modifying enzyme.

15. Claims 1-3, 5, 10, 12-17 and 20 rejected under 35 U.S.C. 102(e) as being anticipated by Shone et al (US Pat. 5,962,637; filing date December 3, 1996), in light of the amendment of claims 1, 17 to define the covalent modification to exclude proteolytic cleavage and farnesyl covalent modifications.

16. Claims 1-7, 12-18, 20-21 rejected under 35 U.S.C. 102(e) as being anticipated by Bronstein et al (US Pat. 6,243,980), in light of the amendment of claims 1, 17 to define the covalent modification to exclude proteolytic cleavage and farnesyl covalent modifications.

17. Claim 17 rejected under 35 U.S.C. 102(e) as being anticipated by Kilburn et al (US Pat. 5,962,289), in light of the amendment of claims 1, 17 to define the covalent modification to exclude proteolytic cleavage and farnesyl covalent modifications, in light of the amendment of claims 1, 17 to define the covalent modification to exclude proteolytic cleavage and farnesyl covalent modifications.

18. Claim 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Shone et al as applied to claims 1-3, 5, 10, 12-17 and 20 above, in view of Taremi et al (US Pat. 5,981,167), in light of the amendment of claims 1, 17 to define the covalent modification to exclude proteolytic cleavage and farnesyl covalent modifications.

19. Claims 8 rejected under 35 U.S.C. 103(a) as being unpatentable over Shone et al as applied to claims 1-3, 5, 10, 12-17 and 20 above, in view of Little et al (US Pat. 6,322,970), in light of the amendment of claims 1, 17 to define the covalent modification to exclude proteolytic cleavage and farnesyl covalent modifications.

New Combination of Claim Limitations/New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 112

20. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Claims 1-12, 14-15, 17-18 and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

All of the claims have been amended to require the covalent modification to be one of : phosphylation, acylation, gernaylation, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation or the reversal of any one of these covalent modification and the determining of the presence of the modifying enzyme is through the presence of the covalent modification in the first or second polypeptides that are associated through the covalent modification.

The first and second polypeptides are not provided in a form that comprise any of the recited covalent modifications and therefore do not enable the reversal of any one of the covalent modifications recited in the claims. The reversal of a covalent modification must act upon a substrate that comprises the covalent modification and neither the first or second polypeptide are defined to comprise the phosphylation, acylation, gernaylation, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation groups required for modifying enzyme activity. The

claims are not enabled for the detection of an enzyme in a sample based upon the reversal of a covalent modification that is not present in one of the polypeptide. The "wherein" clause defines the covalent modification in the further tense by reciting "wherein"... "covalent modification of at least one of the polypeptides results in the modulation of the association", thus the claim does not define the polypeptides to comprise the covalent modification groups of newly amended claim 1, and the reversal of the covalent modification can not be carried out with a functional group that is not present.

With respect to the covalent modification of a either one of the polypeptides, with any one of the recited groups: phosphylation, acylation, gernaylation, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation, would require the functional group to be provided or present in the sample. None of the groups are provided or defined to be present in the sample used to contact the first and second polypeptides. Enzymatic action and covalent modification of either the first or second polypeptides would not take place in the absence of the functional group used to modify.

The detection of the presence of a modifying enzyme is not enabled in the absence of the modifying group being present in the sample which would provide for the association of the first and second polypeptides. No association of the first and second polypeptides would take place, even in the presence of the enzyme in the sample, when the modifying group being one used for phosphylation, acylation, gernaylation, glycosylation, ubiquitination, prenylation, sentrinization, or ADP-ribosylation is not provided.

The source and type of sample has not been defined to be one that would contain any of the recited modifying groups; the sample has not been defined to serve as a source of the modifying groups in a form that would permit detection of the association. Neither the first and second polypeptides are defined to be covalently modified/labeled in any way. How the association is measured in the absence of the covalent modification has not been defined to be one that is determinable by the language set forth in the claims.

The combination of claim limitation set forth in the newly amended claims is not enabled for the detection of a modifying enzyme that causes phosphylation, acylation, gernaylation, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation as the assay is completely lacking in the groups upon which the enzymes act to cause covalent modification.

22. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 12 recites a combination of claim limitations the sets forth an antibody that binds to either the first or second polypeptides, and not the association of the first and second polypeptides based upon the covalently modified combination of the first and second polypeptides, the modification being phosphylation, acylation, gernaylation, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation. The antibody is not directed to binding the covalent modification functional group (newly amended combination of claim limitations) used to modify the association of the first and

second polypeptides. The antibody only binds to the first or second polypeptides and not the group used for phosphylation, acylation, gernaylation, glycosylation, ubiquitination, prenylation, sentrinization, or ADP-ribosylation. Thus the presence of the modifying enzyme which is detected based upon the covalent modification of one of the polypeptides with an antibody that only binds to the polypeptide portion and not the covalent modification in either one of the polypeptides, does not enable the detection of the enzyme in a sample, as the antibody would bind to either polypeptide whether the enzyme is present or not, and binding of the antibody would not be a direct or indirect indicator of an enzyme in a sample.

23. Claim 4, 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 defines the presence of two labels and depends from claim 3 recites the phrase "a label" and amended claim 1 that only measures the association. As the polypeptide and the binding partner are associated and have formed a complex by binding one to the other, there is only a single label associated with the two molecules as both molecules have not been defined in claim 3 to be labeled, but must only be associated with a label; association can be direct or indirect association, specifically indirect association through formation of a complex with a directly labeled binding partner. The recitation of the combination of claim limitations set forth in claims 1, 3 and 4 is confusing as what is measured in amended claim 1, has not been defined to be two

different labels, nor have claims 2 or 3 defined the presence of two labels. While the claim language set forth in claim 4 defines the presence of two labels, claim 4 is unclear from depending from claims that only recite the presence of a single label; "a label (claims 2 and 3)".

Claim 20 broadens the scope of claim 1 by reciting the phrase "an enzymatic modification" , while claim 1 has been amended to recite specific type of enzymatic covalent modification; claim 20 is not further limiting of claim 1.

Conclusion

24. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Branch et al (US Pat. 6,235,466) is cited to show Instant claims 1 and 21 directed to a method of detecting an enzyme in a sample (see Branch et al, claims 11-17), the comprising the steps of:

providing first (anti-enzyme antibody, see claim 11, paragraph (A)) and second (see anti-phosphotyrosine antibody) polypeptides that are capable of associating upon the covalent modification (tyrosine phosphylation of the first polypeptide in the immune complex of the first polypeptide and the enzyme) of one of the first and second polypeptides;

immobilizing the first polypeptide to a physical support (see claim 11, paragraph (a) and enolase (polypeptide on the solid phase, see figure 6);

contacting the immobilized polypeptide with the second, binding partner polypeptide (see claim 11, paragraph (B), sub-paragraph (a) (I);

contacting the immobilized polypeptide and the second polypeptide with a sample (see claim 11, paragraph (B);

measuring the association of the second binding partner polypeptide to the first polypeptide, thereby determining the modification of the first polypeptide (immune complex detected with labeled second polypeptide bound to the first polypeptide/enzyme immune complex: see Branch et al, claim 11, paragraphs (B) and (C) and subparagraphs, especially subparagraph (B)(c) (ii), thereby determining the covalent modification of the polypeptide and the presence of the modifying enzyme in the sample.

Instant claim 2: wherein one of the polypeptides is associated with a label (the second polypeptide is labeled; see claim 11, paragraph (B)(a)(I).

Instant claim 3: wherein both the immobilized polypeptide and the second polypeptides are associated with a label (the immune complex is associated with a label; see claim 11, paragraph (B)(c)(I and ii).

Instant claim 5: wherein the label is fluorescent (see Branch et al, claim 11, paragraph (B)(a)(I).

Instant claim 10:wherein the label is a radioactive label (see Branch et al, claim 11, paragraph (B)(a)(I).

Instant claim 12:wherein the association is measured with an antibody (see Branch et al, claim 11, paragraph (B)(a)(iii) and (c)(ii).

Instant claim 14: wherein the immobilized polypeptide is covalently modified (see Figure 6, E^{-p}, phosphorylated enolase and phosphorylated PTK.

Instant claim 20: wherein the covalent modification is an enzyme modification (see Branch et al, claims 11-15).

Instant claim 21: comparing the measured results to a positive control (see col. 5, lines 28-32 and claim 11, paragraph (C)(c).

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

26.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

May 1, 2003

LYNETTE R. F. SMITH
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